

a) contacting said candidate compound with a mammalian cell which expresses on its surface a recombinant high-affinity melatonin receptor protein or melatonin binding fragment or analog thereof;

b) measuring binding between (1) said receptor protein, or melatonin binding fragment or analog thereof, and (2) melatonin; and

c) where said contacting causes a decrease in said binding, identifying said candidate compound as an antagonist of a high affinity melatonin receptor ligand [where said contacting causes a decrease in binding between said recombinant high-affinity melatonin receptor protein and melatonin].

35. (Amended) The method of claim 33, wherein said [cell is a] mammalian cell is transfected with an expression vector encoding the receptor protein or fragment or analog thereof, and wherein in the absence of the expression vector, the mammalian cell [which normally] presents substantially no high-affinity melatonin receptor on its surface.

Add new claims 37-77:

--37. A method of testing a candidate compound for the ability to act as an agonist of a high affinity melatonin receptor ligand, said method comprising:

a) contacting said candidate compound with a cell comprising an expression vector encoding a high-affinity melatonin receptor protein comprising an amino acid sequence substantially identical to SEQ ID NO:2, or a melatonin binding fragment or analog thereof, wherein the cell expresses on its surface said high-affinity melatonin receptor protein or melatonin binding fragment or analog thereof;

b) measuring intracellular cAMP concentration in said cell; and

c) where said contacting causes a decrease in intracellular cAMP concentration, identifying said candidate compound as an agonist of a high affinity melatonin receptor ligand.

38. A method of testing a candidate compound for the ability to act as an antagonist of a high affinity melatonin receptor ligand, said method comprising:

a) contacting said candidate compound with a cell comprising an expression vector encoding a high-affinity melatonin receptor protein comprising an amino acid sequence substantially identical to SEQ ID NO:2, or a melatonin binding fragment or analog thereof, wherein the cell expresses on its surface said high-affinity melatonin

receptor protein or melatonin binding fragment or analog thereof;

b) measuring binding between (1) said high-affinity melatonin receptor protein, or melatonin binding fragment or analog thereof, and (2) melatonin; and

c) where said contacting causes a decrease in said binding, identifying said candidate compound as an antagonist of a high affinity melatonin receptor ligand.

39. The method of claim 37, wherein the receptor protein consists of the amino acid sequence of SEQ ID NO:2.

40. The method of claim 38, wherein the receptor protein consists of the amino acid sequence of SEQ ID NO:2.

41. A method of testing a candidate compound for the ability to act as an agonist of a high affinity melatonin receptor ligand, said method comprising:

a) contacting said candidate compound with a cell comprising an expression vector encoding a high-affinity melatonin receptor protein, wherein the expression vector comprises a sequence that hybridizes under conditions of high stringency to a probe having the sequence of the complement of SEQ ID NO:1;

b) measuring intracellular cAMP concentration in said cell; and

c) where said contacting causes a decrease in intracellular cAMP concentration, identifying said candidate compound as an agonist of a high affinity melatonin receptor ligand.

42. A method of testing a candidate compound for the ability to act as an antagonist of a high affinity melatonin receptor ligand, said method comprising:

a) contacting said candidate compound with a cell comprising an expression vector encoding a high-affinity melatonin receptor protein, wherein the expression vector comprises a sequence that hybridizes under conditions of high stringency to a probe having the sequence of the complement of SEQ ID NO:1;

b) measuring binding between (1) said high-affinity melatonin receptor protein, or melatonin binding fragment or analog thereof, and (2) melatonin; and

c) where said contacting causes a decrease in said binding, identifying said candidate compound as an antagonist of a high affinity melatonin receptor ligand.

43. The method of claim 41, wherein the expression vector comprises the sequence of SEQ ID NO:1.

44. The method of claim 42, wherein the expression vector comprises the sequence of SEQ ID NO:1.

45. A method of testing a candidate compound for the ability to act as an agonist of a high affinity melatonin receptor ligand, said method comprising:

- a) contacting said candidate compound with a mammalian cell comprising an expression vector encoding a high-affinity melatonin receptor protein comprising an amino acid sequence substantially identical to SEQ ID NO:4, or a melatonin binding fragment or analog thereof, wherein the cell expresses on its surface said high-affinity melatonin receptor protein or melatonin binding fragment or analog thereof;
- b) measuring intracellular cAMP concentration in said cell; and
- c) where said contacting causes a decrease in intracellular cAMP concentration, identifying said candidate compound as an agonist of a high affinity melatonin receptor ligand.

46. A method of testing a candidate compound for the ability to act as an antagonist of a high affinity melatonin receptor ligand, said method comprising:

- a) contacting said candidate compound with a mammalian cell comprising an expression vector encoding a high-affinity melatonin receptor protein comprising an amino acid sequence substantially identical to SEQ ID NO:4, or a melatonin binding fragment or analog thereof, wherein the cell expresses on its surface said high-affinity melatonin receptor protein or melatonin binding fragment or analog thereof;
- b) measuring binding between (1) said high-affinity melatonin receptor protein, or melatonin binding fragment or analog thereof, and (2) melatonin; and
- c) where said contacting causes a decrease in said binding, identifying said candidate compound as an antagonist of a high affinity melatonin receptor ligand.

47. The method of claim 45, wherein the receptor protein consists of the amino acid sequence of SEQ ID NO:4.

48. The method of claim 46, wherein the receptor protein consists of the amino

acid sequence of SEQ ID NO:4.

49. A method of testing a candidate compound for the ability to act as an agonist of a high affinity melatonin receptor ligand, said method comprising:

- a) contacting said candidate compound with a cell comprising an expression vector encoding a high-affinity melatonin receptor protein, wherein the expression vector comprises a sequence that hybridizes under conditions of high stringency to a probe having the sequence of the complement of SEQ ID NO:3;
- b) measuring intracellular cAMP concentration in said cell; and
- c) where said contacting causes a decrease in intracellular cAMP concentration, identifying said candidate compound as an agonist of a high affinity melatonin receptor ligand.

50. A method of testing a candidate compound for the ability to act as an antagonist of a high affinity melatonin receptor ligand, said method comprising:

- a) contacting said candidate compound with a cell comprising an expression vector encoding a high-affinity melatonin receptor protein, wherein the expression vector comprises a sequence that hybridizes under conditions of high stringency to a probe having the sequence of the complement of SEQ ID NO:3;
- b) measuring binding between (1) said high-affinity melatonin receptor protein, or melatonin binding fragment or analog thereof, and (2) melatonin; and
- c) where said contacting causes a decrease in said binding, identifying said candidate compound as an antagonist of a high affinity melatonin receptor ligand.

51. The method of claim 49, wherein the expression vector comprises the sequence of SEQ ID NO:3.

52. The method of claim 50, wherein the expression vector comprises the sequence of SEQ ID NO:3.

53. A method of testing a candidate compound for the ability to act as an agonist of a high affinity melatonin receptor ligand, said method comprising:

- a) contacting said candidate compound with a cell comprising an expression

vector encoding a high-affinity melatonin receptor protein comprising an amino acid sequence substantially identical to SEQ ID NO:12, or a melatonin binding fragment or analog thereof, wherein the cell expresses on its surface said high-affinity melatonin receptor protein or melatonin binding fragment or analog thereof;

- b) measuring intracellular cAMP concentration in said cell; and
- c) where said contacting causes a decrease in intracellular cAMP concentration, identifying said candidate compound as an agonist of a high affinity melatonin receptor ligand.

54. A method of testing a candidate compound for the ability to act as an antagonist of a high affinity melatonin receptor ligand, said method comprising:

- a) contacting said candidate compound with a cell comprising an expression vector encoding a high-affinity melatonin receptor protein comprising an amino acid sequence substantially identical to SEQ ID NO:12, or a melatonin binding fragment or analog thereof, wherein the cell expresses on its surface said high-affinity melatonin receptor protein or melatonin binding fragment or analog thereof;
- b) measuring binding between (1) said high-affinity melatonin receptor protein, or melatonin binding fragment or analog thereof, and (2) melatonin; and
- c) where said contacting causes a decrease in said binding, identifying said candidate compound as an antagonist of a high affinity melatonin receptor ligand.

55. The method of claim 53, wherein the receptor protein consists of the amino acid sequence of SEQ ID NO:12.

56. The method of claim 54, wherein the receptor protein consists of the amino acid sequence of SEQ ID NO:12.

57. A method of testing a candidate compound for the ability to act as an agonist of a high affinity melatonin receptor ligand, said method comprising:

- a) contacting said candidate compound with a cell comprising an expression vector encoding a high-affinity melatonin receptor protein, wherein the expression vector comprises a sequence that hybridizes under conditions of high stringency to a probe having the sequence of the complement of SEQ ID NO:11;
- b) measuring intracellular cAMP concentration in said cell; and

c) where said contacting causes a decrease in intracellular cAMP concentration, identifying said candidate compound as an agonist of a high affinity melatonin receptor ligand.

58. A method of testing a candidate compound for the ability to act as an antagonist of a high affinity melatonin receptor ligand, said method comprising:

a) contacting said candidate compound with a cell comprising an expression vector encoding a high-affinity melatonin receptor protein, wherein the expression vector comprises a sequence that hybridizes under conditions of high stringency to a probe having the sequence of the complement of SEQ ID NO:11;

b) measuring binding between (1) said high-affinity melatonin receptor protein, or melatonin binding fragment or analog thereof, and (2) melatonin; and

c) where said contacting causes a decrease in said binding, identifying said candidate compound as an antagonist of a high affinity melatonin receptor ligand.

59. The method of claim 57, wherein the expression vector comprises the sequence of SEQ ID NO:11.

60. The method of claim 58, wherein the expression vector comprises the sequence of SEQ ID NO:11.

61. A method of testing a candidate compound for the ability to act as an agonist of a high affinity melatonin receptor ligand, said method comprising:

a) contacting said candidate compound with a cell comprising an expression vector encoding a high-affinity melatonin receptor protein comprising an amino acid sequence substantially identical to SEQ ID NO:14, or a melatonin binding fragment or analog thereof, wherein the cell expresses on its surface said high-affinity melatonin receptor protein or melatonin binding fragment or analog thereof;

b) measuring intracellular cAMP concentration in said cell; and

c) where said contacting causes a decrease in intracellular cAMP concentration, identifying said candidate compound as an agonist of a high affinity melatonin receptor ligand.

62. A method of testing a candidate compound for the ability to act as an antagonist of a high affinity melatonin receptor ligand, said method comprising:

a) contacting said candidate compound with a cell comprising an expression vector encoding a high-affinity melatonin receptor protein comprising an amino acid sequence substantially identical to SEQ ID NO:14, or a melatonin binding fragment or analog thereof, wherein the cell expresses on its surface said high-affinity melatonin receptor protein or melatonin binding fragment or analog thereof;

b) measuring binding between (1) said high-affinity melatonin receptor protein, or melatonin binding fragment or analog thereof, and (2) melatonin; and

c) where said contacting causes a decrease in said binding, identifying said candidate compound as an antagonist of a high affinity melatonin receptor ligand.

63. The method of claim 61, wherein the receptor protein consists of the amino acid sequence of SEQ ID NO:14.

64. The method of claim 62, wherein the receptor protein consists of the amino acid sequence of SEQ ID NO:14.

65. A method of testing a candidate compound for the ability to act as an agonist of a high affinity melatonin receptor ligand, said method comprising:

a) contacting said candidate compound with a cell comprising an expression vector encoding a high-affinity melatonin receptor protein, wherein the expression vector comprises a sequence that hybridizes under conditions of high stringency to a probe having the sequence of the complement of SEQ ID NO:13;

b) measuring intracellular cAMP concentration in said cell; and

c) where said contacting causes a decrease in intracellular cAMP concentration,

identifying said candidate compound as an agonist of a high affinity melatonin receptor ligand.

66. A method of testing a candidate compound for the ability to act as an antagonist of a high affinity melatonin receptor ligand, said method comprising:

- a) contacting said candidate compound with a cell comprising an expression vector encoding a high-affinity melatonin receptor protein, wherein the expression vector comprises a sequence that hybridizes under conditions of high stringency to a probe having the sequence of the complement of SEQ ID NO:13;
- b) measuring binding between (1) said high-affinity melatonin receptor protein, or melatonin binding fragment or analog thereof, and (2) melatonin; and
- c) where said contacting causes a decrease in said binding, identifying said candidate compound as an antagonist of a high affinity melatonin receptor ligand.

67. The method of claim 65, wherein the expression vector comprises the sequence of SEQ ID NO:13.

68. The method of claim 66, wherein the expression vector comprises the sequence of SEQ ID NO:13.

69. A method of testing a candidate compound for the ability to act as an agonist of a high affinity melatonin receptor ligand, said method comprising:

- a) contacting said candidate compound with a cell comprising an expression vector encoding a high-affinity melatonin receptor protein comprising an amino acid sequence substantially identical to SEQ ID NO:16, or a melatonin binding fragment or analog thereof, wherein the cell expresses on its surface said high-affinity melatonin receptor protein or melatonin binding fragment or analog thereof;
- b) measuring intracellular cAMP concentration in said cell; and
- c) where said contacting causes a decrease in intracellular cAMP concentration, identifying said candidate compound as an agonist of a high affinity melatonin receptor



ligand.

70. A method of testing a candidate compound for the ability to act as an antagonist of a high affinity melatonin receptor ligand, said method comprising:

- a) contacting said candidate compound with a cell comprising an expression vector encoding a high-affinity melatonin receptor protein comprising an amino acid sequence substantially identical to SEQ ID NO:16, or a melatonin binding fragment or analog thereof, wherein the cell expresses on its surface said high-affinity melatonin receptor protein or melatonin binding fragment or analog thereof;
- b) measuring binding between (1) said high-affinity melatonin receptor protein, or melatonin binding fragment or analog thereof, and (2) melatonin; and
- c) where said contacting causes a decrease in said binding, identifying said candidate compound as an antagonist of a high affinity melatonin receptor ligand.

71. The method of claim 69, wherein the receptor protein consists of the amino acid sequence of SEQ ID NO:16.

72. The method of claim 70, wherein the receptor protein consists of the amino acid sequence of SEQ ID NO:16.

73. A method of testing a candidate compound for the ability to act as an agonist of a high affinity melatonin receptor ligand, said method comprising:

- a) contacting said candidate compound with a cell comprising an expression vector encoding a high-affinity melatonin receptor protein, wherein the expression vector comprises a sequence that hybridizes under conditions of high stringency to a probe having the sequence of the complement of SEQ ID NO:15;
- b) measuring intracellular cAMP concentration in said cell; and
- c) where said contacting causes a decrease in intracellular cAMP concentration, identifying said candidate compound as an agonist of a high affinity melatonin receptor ligand.

74. A method of testing a candidate compound for the ability to act as an antagonist of a high affinity melatonin receptor ligand, said method comprising:

a) contacting said candidate compound with a cell comprising an expression vector encoding a high-affinity melatonin receptor protein, wherein the expression vector comprises a sequence that hybridizes under conditions of high stringency to a probe having the sequence of the complement of SEQ ID NO:15;

b) measuring binding between (1) said high-affinity melatonin receptor protein, or melatonin binding fragment or analog thereof, and (2) melatonin; and

c) where said contacting causes a decrease in said binding, identifying said candidate compound as an antagonist of a high affinity melatonin receptor ligand.

75. The method of claim 73, wherein the expression vector comprises the nucleotide sequence of SEQ ID NO:15.

76. The method of claim 74, wherein the expression vector comprises the nucleotide sequence of SEQ ID NO:15.

77. The method of claim 34, wherein said mammalian cell is transfected with an expression vector encoding the receptor protein or fragment or analog thereof, and wherein in the absence of the expression vector, the mammalian cell presents substantially no high-affinity melatonin receptor on its surface.--

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REMARKS

Claims 33-35 and 37-77 are pending, claims 37-77 having been added by the above amendment.

Support for the amendment to claims 33-35 appears in the specification on page 8, lines 20-29.

Support for new claims 37, 39, 45, 47, 53, 55, 61, 63, 69, and 71 appears in the specification on page 3, lines 18-31; page 5, lines 7-22; page 7, lines 14-32; page 8, lines 20-29;